

PATENT
Customer No. 22,852
Attorney Docket No. 09797.0004-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Lieven J. STUYVER et al.) Group Art Unit: 1623
Application No.: 10/045,292) Examiner: Traviss C. McIntosh, III
Filed: October 18, 2001)
For: MODIFIED NUCLEOSIDES FOR) Confirmation No.: 4833
THE TREATMENT OF VIRAL)
INFECTIONS AND ABNORMAL)
CELLULAR PROLIFERATION)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

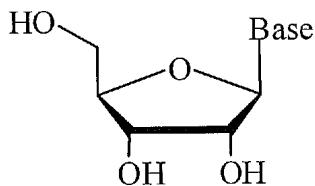
DECLARATION

I, Michael J. Otto, Ph.D., a U.S. citizen, residing at 28 Eastwood Drive, East Windsor, NJ 08520, declare:

1. I have a Ph.D. in Medical Microbiology from the Medical College of Wisconsin, with a specialization in molecular virology and antiviral drugs. I have worked in antiviral drug discovery research and development since 1980. During this time I have published over 80 papers describing the efficacy and mechanism of action several classes of antiviral drugs including nucleoside analogs.

2. I have read the Office Action issued against the above-identified application on September 11, 2008, and the reference cited therein, WO 98/18324 to Loeb, et al. ("Loeb").

3. Loeb is directed to the identification and use of naturally occurring ribonucleoside analogs to induce one or more mutations in an RNA virus in order to inhibit viral replication. Loeb describes how naturally occurring ribonucleosides where the 2', 3', and 5' positions of the ribose are substituted with -OH can be incorporated and extended by a polymerase. Loeb at 22, 25.



Nucleosides as described in the present application inhibit the replication of viruses by a different mechanism than that described by Loeb.

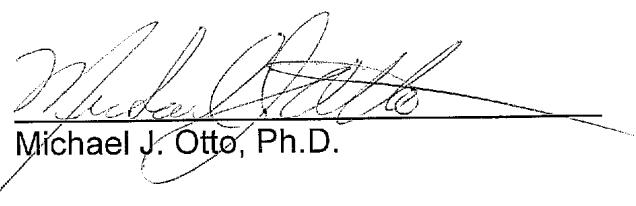
4. The nucleosides described by Loeb are incorporated into the newly synthesized RNA and exert their effects by causing errors in subsequent copying of this RNA. Thus, the nucleosides of Loeb do not inhibit RNA polymerase. The nucleosides described in the present application act directly to inhibit the enzymes responsible for copying the RNA. Once metabolized into nucleotides and incorporated, these nucleosides, because of the substitutions on the sugar and/or base portions, cause the incorporation process to be terminated immediately following the newly incorporated nucleotide. No mutational event occurs during this type of inhibition.

5. At the time the above-identified application was filed, it would not have been obvious from Loeb that deoxyribose and dideoxyribose nucleosides could be used to treat *Flaviviridae*, *Orthomyxoviridae*, or *Paramyxoviridae* infections, since these viruses are RNA viruses that do not have a DNA phase as part of their life cycle.

6. Nucleosides as described in the present application are metabolized to their corresponding triphosphate forms which are recognized by the RNA polymerases of *Flaviviridae*, *Orthomyxoviridae*, and *Paramyxoviridae* viral infections. These enzymes incorporate the nucleotides resulting in the termination of the replicative process. This effectively stops the viruses from causing further infection and results in the effective therapy for these infections. Data related to *Flaviviridae* viral infections are reported for compounds AI, AT, BE, BO and CM in Table 21, compounds AI, AT, BE, and BO in Table 24, and compounds AI, AT, and BE in Table 25. See Examples 55 and 59 in the as-filed specification. Data related to respiratory viruses are reported for compound AJ in Table 23. See Example 58 in the as-filed specification.

The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true. Furthermore, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 9th day of March, 2009.


Michael J. Otto, Ph.D.